to anesthesia and TS mice showed increased sensitivity to anesthetic (ketamine) with much loner QT prolongation and arrhythmias such as premature beats and apparent AV block.

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Ranolazine Antagonizes The Effects Of Anemone Toxin-II On Intracellular Ca2+ Cycling In Whole Heart

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The late sodium current (INa,L) is pathologically enhanced in several cardiac disease states, including ischemia, causing increased intracellular Na+ and Ca2+ loading and cellular dysfunction. Ranolazine (RAN) is a blocker of INa,L and this mechanism is thought to underlie its effectiveness at reversing many of the cellular effects of ischemia. The goal of this study was to determine if RAN antagonizes the effect of anemone toxin II (ATX-II), an INa,L enhancer known to increase Na+ influx, to alter intracellular Ca2+ cycling in individual myocytes of intact heart. Langendorff-perfused rat hearts were loaded with fluo-4AM (15μM) and placed in a chamber on the stage of a confocal microscope (contractions abolished with cytochalasin-D and blebbistatin). ATX-II (1nM) prolonged the early phase[j1] of basal Ca2+ transients (CaTs) in cells of hearts paced at a rate of 2 Hz[j2]. ATX-II slowed the rate of recovery of cellular CaTs (i.e., restitution) and promoted the development of CaT alternans at slower pacing rates. RAN (10μM) partially reversed the effects of ATX on restitution and alternans, shifting both to shorter intervals[j3] . In addition, pre-treatment with RAN reduced the effects of subsequent exposure to ATX-II on both restitution and alternans development and blunted the ATX-induced changes in basal CaTs. These effects are consistent with an action of RAN to block $I_{Na,L}$, reducing Na^+ influx and resulting intracellular Ca^{2+} accumulation, and therefore suggest RAN treatment may reverse the effects of Ca^{2+} accumulation that occur in response to disease states in which $I_{Na,L}$ is enhanced (such as ischemia). Consequently, RAN may also reduce the arrhythmias that might result from repolarization gradients established by Ca2+ alternans and the resulting action potential duration alternans.

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NS5806 Activates the Transient Outward Potassium Current in the Canine Ventricle and Provides a New Model of the Brugada Syndrome

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Background: The Brugada syndrome (BrS) is characterized by elevated ST segments in the right precordial leads, ventricular tachycardia and sudden death. The syndrome has been linked to loss-of-function of sodium and calcium channels, however the transient outward potassium current (Ito) is thought to be central in the pathogenesis of BrS. We assessed the effects of Ito augmentation in a mammalian model using a novel activator of Ito, NS5806. Methods and Results: Voltage-clamp experiments were performed on midmyocardial cells isolated from the canine left ventricular wall. At 40mV NS5806 (10 μM) increased peak Ito by 79 ± 4 % and the time-course of inactivation was slowed (from Tau=12.6 ± 3.2 ms to 20.3 ± 2.9 ms). We next assessed the effect of increased Ito in the development of BrS phenotype using canine ventricular wedge preparations. NS5806 increased the epicardial action potential (AP) phase 1 magnitude, whereas the APs of endocardial cells were largely unaffected. The accentuated epicardial notch was associated with an accentuated J-wave on the ECG. Loss of the epicardial AP dome at some sites but not others, led to development of phase-2-reentry and polymorphic ventricular tachycardia. NS5806 was able to induce the BrS phenotype in wedges from both right and left ventricles of the canine heart; at 15 μM NS5806 BrS developed in 4/6 right ventricular preparations compared to 2/10 left ventricular preparations. Conclusion: The Ito agonist NS5806 recapitulates the electrographic and arrhythmic manifestation of BrS, providing evidence in support of its pivotal role in the genesis of the disease. Our findings suggest that a genetic defect leading to a prominent gain of function of Ito could explain variants of BrS in which ST segment elevation are evident in both right and left ECG leads.

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Chaos Synchronization in the Genesis of Cardiac Arrhythmias

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Afterdepolarizations resulting from interactions between membrane voltage and intracellular calcium cycling are considered to play a key role in arrhythmias in long-QT syndromes (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), heart failure and other conditions. Although the molecular pathophysiology of early afterdepolarizations (EADs) at the cellular level has been analyzed in many studies, how EADs lead to triggered activity in cardiac tissue remains a major unsolved question. Specifically, due to the source-sink mismatch, a single myocyte which is well-coupled to adjacent myocytes cannot manifest an overt EAD unless a critical mass of the adjacent myocytes also simultaneously decide to exhibit EADs, What then synchronizes EADs in a critical mass of myocytes? In this study, we present evidence from isolated myocytes exposed to hydrogen peroxide (H2O2) that EAD dynamics during periodic pacing are chaotic, rather than random. Using computer simulations, we demonstrate that electronic interactions between adjacent myocytes can cause local synchronization of chaotic EADs over a characteristic length scale, producing groups of myocytes with overt EADs next to groups of myocytes without EADs when the tissue exceeds a critical size. The resulting gradients in refractoriness allow EADs to propagate, which can then stimulate other regions to develop EADs, creating a tissue network of multifocal triggered activity. Local conduction block across refractory gradients can also initiate reentry. The electrocardiographic pattern is polymorphic ventricular tachycardia (PVT). In optically-mapped rabbit ventricles, we observed activation patterns during H2O2-induced EADs and PVT showing a mixture of focal activity and reentry, consistent with this chaos synchronization mechanism. Chaos synchronization is a novel mechanism for cardiac arrhythmogenesis which may account for lethal arrhythmias appearing suddenly during bradycardia.

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Assembling And Imaging Long Cables Of Live Cardiomyocytes For Validation Of Cable Theory Relationships

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Theoretical work on excitable tissue (heart, brain, muscle) often employs concepts from cable theory and resorts to one-dimensional models of wave propagation for capture of essential functional properties. We offer an experimental technique to spatially pack, image and computationally unpack quasi-one dimensional long cables (>10cm) of live excitable cells within the imaging field of view. This is achieved by micropatterning neonatal rat cardiomyocytes into Archimedean spiral topologies and imaging the whole cable at ultra-high resolution. We validate the method's applicability to studies of wave propagation assessing distortions due to curvature effects.

Specific demonstrations of the utility of the proposed method include experimental verification of the eikonal relationship linking the velocity of a wave in homogenous cardiac tissue and the radius of curvature seen by the wavefront. This is achieved by patterning thin cables with well defined linearly varying curvature. Furthermore, the technique is applied to validation of theoretical predictions regarding spatially discordant alternans - beat-to-beat alternations in cardiac signals that can be out-of-phase over space. Previous attempts to uncover mechanisms for spatially discordant alternans have utilized purely computational representations and fluorescence imaging of whole-heart preparations and two-dimensional cardiomyocyte monolayer networks. The cable-like geometry (~10cm) used here facilitate the direct comparison to analytical and numerical derivations done exclusively in 1D.

In conclusion, our experimental approach allows for systematic validation of different aspects of cable theory and various excitable tissue phenomena in a well-controlled setting, including wavefront-waveback interactions, implementations of distributed feedback control strategies etc.

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Gender Difference in Cardiac Repolarization: A Computational Study

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Multiple experimental studies have shown post-pubescent males have shorter QT intervals than females. Clinical studies have revealed that sex differences in QT interval become apparent from puberty, suggesting sex steroid hormones play a role in shortening QT intervals. Testosterone has acute non-transcriptional effects mediated by increased nitric oxide (NO) production, which results in increased slow delayed rectifier K^+ currents (I_{ks}) and reduced L-type Ca^{2+} currents ($I_{Ca,L}$). Like testosterone, progesterone modifies I_{ks} and $I_{Ca,L}$ currents via eNOs production of NO. On the other hand, 17β-estradiol inhibits I_{Kr} current according to very recent experimental results. To investigate effects of sex